Remarks

I. The Examiner Interview

Applicants would like to thank Examiner Riggins and Examiner Ketter for the very helpful personal interview conducted with Dr. Umaña and Applicants' counsel at the USPTO on June 17, 2005. Applicants have amended the claims consistent with the points discussed during the interview. Applicants believe that this Amendment and Reply addresses all of the outstanding objections and rejections and that they may be withdrawn.

II. Status of the Claims

Upon entry of the foregoing amendment, claims 109-139 are pending in the application, with claims 109, 110, and 118 being the independent claims. Claims 86-108 have been canceled and new claims 109-139 added. Claims 1-85 were canceled previously. These changes are believed to introduce no new matter, and their entry is respectfully requested.

III. The Amendments

The new claims are directed to a glycoengineered, recombinant antibody comprising an Fc region containing N-linked oligosaccharides, wherein the antibody has been engineered to have an *increased proportion of nonfucosylated oligosaccharides in the Fc region (i.e., oligosaccharide conformations that lack the fucose residue) compared to the corresponding antibody produced by the same host cell that has not been glycoengineered*, and wherein said antibody has increased Fc mediated cellular cytotoxicity (claim 109) or, alternatively, increased Fc receptor binding affinity (claim

110) as a result of said increased proportion of nonfucosylated oligosaccharides. Support for the new claims can be found *inter alia* in the disclosure as follows:

CLAIM	SUPPORT
109	See, for example, page 37, line 31, through page 38, line 6; page 22, line 33, through page 23, line 3; page 7, lines 21-27; page 8, lines 13-19; and claim 74 as originally filed
110	See, for example, page 21, lines 15-25; and page 37, line 31, through page 38, line 6.
111	See, for example, page 37, line 31, through page 38, line 6; FIG. 9E.
112-115	See, for example, page 7, lines 14-16; page 11, line 1, through page 12, line 15; page 23, lines 12-26.
116	See, for example, page 38, lines 7-14; FIG. 9E.
117-121	See, for example, page 37, line 22, through page 38, line 6; FIG. 9.
122-123	See, for example, page 22, line 33, through page 23, line 26.
124, 135	See, for example, page 12, line 17, through page 15, line 32.
125-129	See, for example, page 22, line 33, through page 23, line 26.
130-132	See, for example, page 37, line 22, through page 38, line 14: FIG. 9.
133, 136	See, for example, Examples 1-6.
134	See, for example, Example 3.
137	See, for example, page 37, lines 19-21.
138	See, for example, page 22, line 33, through page 23, line 11.
139	See, for example, page 13, lines 18-30.

Accordingly, no new matter is believed to have been added by the amendments, and their entry is respectfully requested.

IV. Brief Description of the Invention

As Applicants explained in the Examiner Interview, the presently claimed invention is directed to a glycoengineered, recombinant antibody comprising an Fc region containing N-linked oligosaccharides, wherein the antibody has been engineered to have an *increased proportion of nonfucosylated oligosaccharides in the Fc region compared to the corresponding antibody produced by the same host cell that has not been glycoengineered*, and wherein said antibody has increased Fc mediated cellular cytotoxicity (claim 109) or, alternatively, increased Fc receptor binding affinity (claim 110) as a result of said increased proportion of nonfucosylated oligosaccharides. This invention is the result of Applicants' discovery that the oligosaccharides that occur in the Fc region of antibodies, such as IgG, can be engineered, by a variety of methods, to produce non-naturally occurring *variant* oligosaccharide conformations that have been found to dramatically increase the antibody effector function, such as antibody-dependent cellular cytotoxicity (ADCC), as well as the antibody's affinity for Fc receptors.

Typically, there is heterogenous processing of the core oligosaccharide structures attached at a particular glycosylation site, so that even monoclonal antibodies exist as multiple glycoforms. By engineering the host cells that produce the antibodies to favor production of an antibody having a variant oligosaccharide conformation in the Fc region, *i.e.*, having a significant increase in the proportion of nonfucosylated oligosaccharide structures, Applicants are able to generate variant glycoforms of the antibody having oligosaccharide conformations that are *not capable of being produced by the host cell absent the glycoengineering* and which exhibit dramatically increased

ADCC and Fc receptor binding compared to the corresponding nonglycoengineered antibody.

The present inventors are believed to be the first ever to demonstrate that antibodies having human Fc regions can be glycoengineered to manipulate the oligosaccharides structures in the Fc region to produce variant glycoforms that are shown to directly correlate with significant increases in ADCC and Fc receptor binding affinity.

V. The Objections to the Specification

At page 2 of the Office Action, the Office has objected to the specification for various informalities. Without acquiescing in the propriety of the rejection, and solely in the interest of advancing prosecution, Applicants have amended the specification in the manner suggested by the Office to address the informalities. Accordingly, reconsideration and withdrawal of the objections are respectfully requested.

VI. The Rejections

A. The Rejection Under 35 U.S.C. 112, First Paragraph

At page 3 of the Office Action, the Office has rejected claim 87 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Office states that claim 87 contains subject matter that is not described in the specification in such a way as to enable one of ordinary skill in the art to make and/or use the invention. At page 5, the Office also rejects claims 88-107 for lack of enablement, on the ground that those claims all depend from rejected claim 87. Applicants respectfully traverse the rejection.

As noted by the Office, claim 87 is directed to glycoengineered antibodies having increased affinity for Fc receptors. In rejecting this claim, the Office asserts that "no

evidence has been provided that enhanced Fc receptor binding is the mechanism of the enhanced antibody-mediated cell death that is observed." (Office Action at page 3, paragraph 5.) In particular, although the Office acknowledges that the antibody-dependent cellular cytotoxicity observed with the claimed antibodies is known to occur through the engagement of Fc receptors on cells, it asserts that "[t]he specification provides no evidence that the modifications to antibody molecules leads to higher affinity of those modified antibodies for Fc receptors." The Office points to a single sentence of the specification at page 21, lines 24-25, as acknowledging that additional experimentation would be required to ensure that the modified antibodies had increased Fc receptor affinity. Finally, the Office speculates that mechanisms other than increased binding to Fc receptors, such as enhanced complement-mediated cell lysis, could account for the increases in ADCC that are observed with the claimed antibodies. As a result, the Office concludes that "the disclosure does not provide sufficient instruction to the skilled artisan of how to reliably and definitively make an antibody that has an increased affinity for Fc receptors." Applicants respectfully disagree.

At the outset, Applicants note that claims 86-107 have been canceled and replaced with new claims 109-139. However, to the extent the new claims also are directed to glycoengineered antibodies having increased binding affinity for Fc receptors, Applicants will address the merits of the rejection.

The test for whether a claim complies with the enablement standard "requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to *make* and *use* the claimed invention" without undue experimentation. *See* Manual of Patent Examining Procedure (MPEP) § 2164.01 (Eighth ed., rev. May 2004) (emphasis

added). As long as the specification discloses *at least one method for making and using the invention as claimed*, then the enablement requirement is satisfied. *See* MPEP at § 2164.01(b). When this standard is applied to the presently claimed invention, it is clear that the claims are enabled.

The Office does not contend that Applicants' specification does not teach how to make and use glycoengineered antibodies with increased Fc-mediated cellular cytotoxicity. To the contrary, the Office Action expressly acknowledges that the specification is enabling for those antibodies. (Office Action at page 5, paragraph 9.) Rather, the Office's position appears to be that there is no evidence showing that increased binding to Fc receptors is the mechanism through which those antibodies achieve increased Fc-mediated cellular cytotoxicity. This is incorrect.

First, as the Office has acknowledged, it was known that ADCC is mediated through the engagement of Fc receptors on lymphocyte cells. Second, there is no question that the present application specifically identifies engineering the Fc region of antibodies to increase their affinity for lymphocyte receptors as one means to increase ADCC. (*See* page 21, lines 15-17.) The Office cites the use of the term "explored" at page 21, line 24, as evidence that Applicants recognized that further experimentation was needed on the issue. However, this assertion is directly refuted by the context of the sentence in which that term occurs. In particular, after discussing the therapeutic limitations of conventional therapies utilizing unconjugated monoclonal antibodies (page 20, line 30, through page 21, line 14), the Applicants specifically cite engineering the Fc region of such antibodies to increase the affinity for lymphocyte receptors as a way to increase the ADCC. Applicants then immediately go into a discussion of the advantages obtained with the particular glycoengineered constructs described in the working

examples. Moreover, this discussion of increased Fc receptor binding is found in the text of the application coming under the heading "Generation and Use of Antibodies Having Enhanced Antibody-Dependent Cellular Cytotoxicity." Thus, it is clear that the present inventors considered increased Fc receptor binding to be an advantage achieved by the disclosed glycoengineered antibodies.

The Office's contention that increased complement-mediated lysis is one possible explanation for the increase in Fc-mediated cellular cytotoxicity observed with the claimed antibodies is also without merit. This contention appears to be based on the assumption that the cell lysis assays described in the application were performed in serum. This is incorrect. Although the cells producing the antibodies were cultured in serum, the assay in which cell lysis was tested was not performed in serum. Nothing in the applications suggests that the assay was conducted in serum. Thus, the components of the complement system were not present and could not create ambiguity in the ADCC assay. Applicants emphasize that the assay is a standard, art-recognized assay known to be an accurate measure of antibody-mediated cell lysis.

Finally, Applicants have submitted herewith the Declaration Under 37 C.F.R. § 1.132 of Dr. Pablo Umaña, which contains data showing conclusively that glycoengineered antibodies produced according to the methods taught in the application exhibit significantly increased binding to Fc receptors. (*See* Exhibit 1, Declaration Under 37 C.F.R. § 1.132 of Dr. Pablo Umaña, and Exhibits A-D thereto.) Dr. Umaña is currently Chief Scientific Officer and Member of the Board at GlycArt Biotechnology AG in Zurich, Switzerland. He is an expert in the fields of molecular biology and immunology, with particular expertise in the area of antibody engineering, as evidenced by his *curriculum vitae* attached to the Declaration. (*See* Declaration at § 2.)

As noted by Dr. Umaña, the present application teaches that glycoengineered antibodies having increased binding affinity for Fc receptors can be obtained, according to one method, by engineering a host cell to coexpress an antibody and a glycoprotein modifying glycosyltransferase. (*See* Declaration at § 5.) GnTIII and ManII are specifically identified in the application as useful glycoprotein modifying glycosyltransferases for this purpose. (*See* page 13, lines 18-30; page 21, lines 15-25.) In one embodiment, the application teaches that glycoengineered antibodies having increased Fc receptor binding affinity can be obtained by coexpressing the antibody with multiple glycoprotein-modifying glycosyltransferases, e.g., GnTIII + ManII. (*See* Declaration at § 5.)

Exhibits B, C, and D to the Declaration disclose studies in which antibodies coexpressed with wild-type human mannosidase II ("hManII"), wild-type β(1,4)-N-acetylglucosaminyltransferase ("GnTIII"), and hManII + GnTIII, respectively, were assayed for ADCC and Fc receptor binding affinity. In each instance, the glycoengineered antibodies exhibited significantly increased ADCC and Fcγ receptor binding. (*See* Declaration §§ 6-19.) As noted by Dr. Umaña, this evidence demonstrates that glycoengineered antibodies produced according to the techniques taught in the present application exhibit enhanced Fc receptor binding. Thus, contrary to the Office's contention, the present specification did, in fact, enable one of ordinary skill in the art to *make* and *use* the claimed invention as of the filing date.

Accordingly, reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. The Rejection Under 35 U.S.C. § 102 over Lifely et al.

At page 6 of the Office Action, the Office has rejected claims 86-102 and 104-108 under 35 U.S.C. § 102(b) as anticipated by Lifely *et al.*, *Glycobiology 5(8)*:813-822 (1995). Applicants respectfully traverse the rejection.

The Office cites Lifely *et al.* as disclosing CAMPATH-1H antibodies with altered glycosylation patterns. The Office notes that CAMPATH-1H is a humanized IgG and the glycosylation-modified antibodies produced in the Y0 cells of Lifely *et al.* possess enhanced Fc-mediated cellular cytotoxicity. Coincidentally, it is asserted that the antibodies of Lifely *et al.* would *inherently* possess any increase in Fc receptor affinity. (*See* Office Action at page 6, paragraphs 12-13.)

In making the rejection, the Office characterizes the claims as "all product-by-process claims" and states that the determination of patentability is based on the product itself, not the method of production. The Office concludes that "the antibodies produced by Lifely appear to be substantially the same as the antibodies produced in the glycoengineering protocols of the instant application." (Office Action at page 7, paragraph 13.) This is incorrect.

As an initial matter, Applicants note that claims 86-108 have been canceled, and new claims 109-139 added by this Amendment. Nevertheless, to the extent the Office may seek to reject the newly added claims on the same basis as the canceled claims, Applicants will address the merits of the rejection.

First, the Office is incorrect in its characterization of all of the claims as "product-by-process claims." In fact, only claim 108 of the previously pending claims recited process steps. The other claims were all claims to antibody compositions *per se*, and none included limitations restricting the process by which such products are

produced. The newly added claims are similar in this regard, with claims 124 and 133, and the claims dependent thereon, being the only product-by-process claims pending.

It appears that the Office is construing the claim term "glycoengineered" to be a product-by-process limitation. Applicants submit, however, that this is legally improper. Other than the claims noted above, all of the pending claims are directed to a structural entity (i.e., an antibody) that is not defined or limited by a particular process for making it. The term "glycoengineered" is used as an adjective to describe particular structural features of the claimed antibody (i.e., a pattern of Fc region glycosylation that is altered from what is normally observed for the antibody produced by that host cell), not a particular process for producing that altered glycosylation pattern. *See, e.g., Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329-30 (Fed. Cir. 2003) (holding term "non-naturally occurring" does not alone make otherwise pure product claims "product-by-process" claims). Thus, the Office's characterization of the claims as all product-by-process claims is legally improper.

Moreover, Lifely *et al.* do not disclose each and every element of the claimed invention because the claimed antibodies are *structurally distinct* from the antibodies of Lifely *et al.* In particular, Lifely *et al.* does not disclose antibodies having the altered glycosylation required by the current claims. As noted above, the present invention is the result of Applicants' discovery that the oligosaccharides that occur in the Fc region of antibodies, such as IgG, can be engineered, by a variety of methods, to result in *variant oligosaccharide conformations* that have been found to dramatically increase the antibody effector function, such as antibody-dependent cellular cytotoxicity (ADCC), as well as the antibody's affinity for Fc receptors. By engineering the host cells that produce the antibodies to favor production of an antibody having a variant

oligosaccharide conformation in the Fc region, i.e, having a significant increase in the proportion of nonfucosylated oligosaccharide structures, Applicants are able to generate variant glycoforms of the antibody having oligosaccharide conformations that are not normally produced by the host cell absent the glycoengineering. For example, whereas nonglycoengineered antibodies typically have Fc regions containing 10-20% nonfucosylated oligosaccharide structures, Applicants have been able to produce antibody glycosylation variants having greater than 70% nonfucosylated oligosaccharide structures using the glycoengineering techniques taught by the present application. *See* Declaration of Pablo Umaña, Ph.D. at 17. These structurally-distinct glycoengineered antibody variants exhibit dramatically increased ADCC and Fc-receptor binding compared to the corresponding nonglycoengineered antibody produced by the same host cell.

In contrast, Lifely *et al.* merely *compare* the glycosylation and biological activity of antibodies expressed in *different* cells under *different* growth conditions. Lifely *et al.* do not teach the *manipulation of glycosylation* to produce antibody glycovariants having Fc oligosaccharide structures not normally produced by the host cells and having ADCC activity not obtainable in the absence of glycoengineering. The advantages of Applicants' discovery is apparent. The Y0 rat myeloma cells observed by Lifely *et al.* to produce antibodies with enhanced activity are notoriously poor sources of industrial cell lines. However, CHO cells, the preferred industrial cell lines, are identified by Lifely *et al.* as producing antibodies with poor ADCC. Lifely *et al.* provide no guidance whatsoever to one of skill in the art as to how to produce antibody glycovariants having increased ADCC and Fc receptor binding affinity in those same CHO cells. Clearly, a

technology capable of achieving that objective would have significant therapeutic and commercial advantages. Applicants' invention is that technology.

For the above reasons, Applicants respectfully submit that Lifely *et al.* neither teaches nor suggests the presently claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

C. The Rejection Under 35 U.S.C. § 103

At page 7 of the Office Action, the Office has rejected claims 86-108 under 35 U.S.C. § 103(a) as being obvious over Lifely *et al.* in view of Reff, Amstutz, Luiten, Valone, Kaszubowski, Murakami, Mordoh, Shoemaker, Chapman and De Bree. The Office relies on Lifely *et al.* as teaching "antibodies with altered glycosylation patterns that have increased Fc-mediated cellular cytotoxicity, would inherently possess any increases [in] affinity for Fc receptors, and are therapeutic antibodies." The Office relies on the other references to disclose the specific antibodies listed in claim 103. According to the Office, one of skill in the art would have been motivated to enhance the ability of these antibodies according to Lifely to mediate their effector functions, thus it would have been obvious to combine Lifely *et al.* with the other references. Applicants respectfully traverse the rejection.

As discussed in detail above, Lifely *et al.* neither teaches nor suggests all of the limitations of any pending claim. None of the other documents cited by the Office remedies the deficiencies of Lifely *et al.* Specifically, none of the documents teach the *manipulation of glycosylation* to produce antibody glycovariants having Fc oligosaccharide conformations not normally produced by the host cells and having Fc mediated cellular cytotoxicity not otherwise obtainable in the absence of

glycoengineering. Thus, even if the references are combined as suggested by the Office, the claimed invention would not be achieved.

In any event, one of ordinary skill in the art would not be motivated to combine the teachings of Lifely *et al.* with any of the other cited references because Lifely *et al.* explicitly teach that "[i]t would not be safe to extrapolate these results to other antibodies." (Page 820, lines 39-40.) Thus, one of ordinary skill in the art would be discouraged from applying the teachings of Lifely *et al.* to the cited documents disclosing other antibodies. As a result, there would have been no motivation to combine the cited references, and certainly no reasonable expectation of success that such a combination would achieve the claimed invention. Thus, the Office has failed to make out a *prima facie* case of obviousness.

Accordingly, Applicants respectfully submit that the rejection has been addressed and may be withdrawn.

D. Rejection for Double-Patenting

At page 8 of the Office Action, the Office has provisionally rejected various claims for double patenting over claims of Applicants' copending applications. Applicants respectfully request that this rejection be held in abeyance until otherwise allowable claims are identified, at which time Applicants will consider filing a Terminal Disclaimer.

Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Date: July 18, 2005

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